Appendix A

COPY OF SPECIFICATION PARAGRAPHS SHOWING AMENDMENTS

(Deletions are shown by ~~strikethrough~~ and additions are underlined)

Paragraph beginning at page 5, line 10:

Fig. 1A illustrates one embodiment of a bio-assay system in accordance with the present invention.

Fig. 1B illustrates a second embodiment of a bio-assay system in accordance with the present invention.

Paragraph beginning at page 14, line 33:

As illustrated, the system 100 includes a signal source 110, transmission lines 120, a source/detector ground plane 130, a bio-assay device 150, and a signal detector 160. The illustrated embodiment shows two transmission lines 120 coupled to the bio-assay device 150, although in an alternative embodiment, the system may consist of a single transmission line coupled to the bio-assay device for making a single port measurement. Further alternatively, three or more transmission lines may be coupled to the bio-assay device 150 for multiple port measurements.

Paragraph beginning at page 15, line 6:

Transmission lines 120 are formed from a material which can support the propagation of a D.C voltage/current ~~of~~ or an A.C. time or frequency domain signal over the desired frequency of operation. Transmission lines 120 may be realized as a conductive layer, such as a center conductor in a coaxial cable or a gold transmission line, deposited on a substrate, such as alumina, diamond, sapphire, polyimide, or glass using conventional photolithography or semiconductor processing techniques. Signal interconnections 122 may be made via wire/ribbon bonds, soldering, conductive epoxy, connectors, or other conventional connection techniques appropriate for the frequency of operation.

Paragraph beginning at page 15, line 21:

The signal path 152 is designed to provide a low insertion loss medium and can consist of any TE, TM, or TEM signal architecture. In an exemplary embodiment, the signal path 152 consists of a photolithographically formed microstrip transmission line having a sputtered gold thickness on the order of between .1 um to 1000 um. In this embodiment, the transmission line is designed to provide low signal loss from D.C. to 110 GHz. Other conductive materials such as indium tin oxide (ITO), copper, silver, zinc, tin, antimony, gallium, cadmium, chromium, manganese, cobalt, iridium, platinum, mercury, titanium, aluminum, lead, iron, tungsten, nickel, tantalum, rhenium, osmium, thallium or alloys thereof may be used to form the transmission line. In another embodiment, the signal path 152 consists of a dielectric region, further described below.

Paragraph beginning at page 16, line 18:

In the illustrated embodiment, dielectric substrate 151 is located between the signal path ~~151~~ 152 and the bio-assay ground plane 159. However, the MBR 156 and sample 157 may be located proximate to the bio-assay ground plane 159 such that MBR 156 is electromagnetically coupled to the bio-assay ground plane 159 alternatively or in addition to the MBR's location to the signal path 152 as shown in Fig. 1A.

Paragraph beginning at page 16, line 23:

The system 100 includes a signal source 110 which launches a test signal 112 onto the transmission line 120 and towards the bio-assay device 150. A signal detector 160 is positioned along the transmission path to receive the modulated test signal 162 (either reflected or transmitted or both). When the test signal ~~120~~ 112 propagates along the bio-electrical interface region 153 of the bio-assay device 150, the dielectric properties of the MBR 156 modulate the test signal. The modulated test signal 162 is then recovered by the detector 160 and used to detect and identify the molecular binding events occurring within the MBR 156.

Paragraph beginning at page 17, line 17:

As described above, the MBR operates to modulate the test signal. The architecture of the dielectric region 156 serves to signal support propagation through the bio-

electrical interface region without high signal loss. An insulating substrate 176 is used as a binding surface for the MBR in order to form the dielectric region 156 and the MBR may bind either specifically or non-specifically to the insulating substrate 176. The insulating substrate ~~151~~ 176 may consist of the same or different dielectric material as the dielectric substrate 151 and may, alternatively or in addition, consist of linker, matrix, and/or insulating layers further described in the incorporated patent application entitled: "Method and Apparatus for Detecting Molecular Binding Events," serial no. 09/243,194.

Paragraph beginning at page 17, line 30:

As indicated, detection and identification of a ligand is also possible when the ligand is physically separated from but electromagnetically coupled to the signal path ~~151~~ 152. In this instance, the coupling between the signal path ~~151~~ 153 and the suspended ligand will alter the response of the test signal propagating along the signal path ~~151~~ 152, thereby providing a means for detecting and/or identifying ~~it~~ the suspended ligand. The maximum separation between the signal path 151 and suspended ligand is influenced by such factors as the effective dielectric constant of the medium between the signal path 151 and the ligand, the total coupling area, the sensitivity of the signal detector, concentration of the ligands in solution, and the desired detection time. Separation distances are typically on the order of 10^{-1}m, 10^{-2}m 10^{-3}m, 10^{-4}m, 10^{-5}m, 10^{-6}m, 10^{-7}m, 10^{-8}m, 10^{-9}m, 10^{-10}m or range anywhere therebetween.

Paragraph beginning at page 18, line 13:

Molecular binding events occurring within the MBR ~~maybe~~ may be detected and identified using various test systems which generate, recover, and subsequently analyze changes in the generated test signal. Test systems which are capable of use with the present invention include those systems designed to detect changes in the signal's voltage, current, impedance, admittance, reactance, amplitude, phase, delay, frequency, wave shape and/or timing, and other signal properties.

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Paragraph beginning at page 18, line 26:

In one embodiment, measurement system 240 includes an S-Parameter Test Module model no. 8516A 242, a Frequency Synthesizer (not shown) model no. 8341B, and a Vector Network Analyzer model no. 8510B 244, all of which are manufactured by the Hewlett Packard Company of Palo Alto, California (www.hp.com). In this embodiment, measurement system 240 provides a measurement capability between the frequencies of 45 MHz and 40 GHz. In an alternative embodiment, measurement system 240 may consist of model number HP 8751A network analyzer which provides a measurement capability between 5 Hz and 500 MHz. In a further embodiment, measurement system may consist of model number HP 85106D which provides a measurement capability between 33 GHz and 110 GHz, both manufactured by the Hewlett Packard Company. Other measurement systems such as scalar network analyzers, Time Domain Reflectometers, another similar measurement systems may also be used to detect a change in the test signal which is attributable to the dielectric properties of the MBR.

Paragraph beginning at page 20, line 12:

Fig. 3A illustrates in a side view one possible embodiment of the test fixture 300 in accordance with the present invention. Test assembly fixture 300 includes a top plate 302 and a bottom plate 304. Top plate 302 includes ports 350a and 350b for injecting the sample solution. Top plate 302 further includes the top half of a sample cavity 340a. Bottom plate 304 includes the bottom half of the sample cavity 340b. In the preferred embodiment, top and bottom plates 302 and 304 are each composed of machined stainless steel and each measures .0320 cm x 1.575 cm x 3.15 cm. Screws 306 are used to attach top and bottom plates 302 and 304.

Paragraph beginning at page 20, line 33:

Fig. 3B illustrates an end view of the test fixture shown in Fig. 3A. As illustrated, test fixture 300 includes connectors 360a and 360b for communicating signals into and/or out of the test fixture 300. Connectors 360a and 360b are secured to top and bottom plates 302 and 304 via screws 361. Connectors 360a and 360b include center conductors 362 which are coupled to the bio-assay device 400 via transmission lines (not shown) formed between the top and bottom plates 302 and 304, respectively. In the preferred embodiment, connectors 360a and 360b are

SMA connectors such as those manufactured by the SRI Connector Gage Company of Melbourne, Florida (www.sriconnectorgage.com). In alternative embodiments, connectors 360a and 360 b may consist of N, 3.5 mm, 2.9 mm, 2.4 mm or other connectors appropriate for the test frequency range. Fluid ports 350a are used to supply sample to the sample cavity 340.

Paragraph beginning at page 22, line 28:

Fig. 4A illustrates a top view of a standard microstrip transmission line bio-assay 410 for use with the test fixture of Fig. 3A. As illustrated, the signal path consists of a transmission line 412 of width of .065 cm and length of 1.0 cm between the input/output ports 411. Bio-assay 410 is formed using standard photolithographic techniques and fabricated using sputtered gold transmission lines on a .55 mm thick quartz glass substrate 415 having a dielectric constant of approx. 3. Those of skill in the art will appreciate that other signal path architectures, conductive and substrate materials, and photolithographic techniques may be alternatively employed.

Paragraph beginning at page 23, line 24:

In the illustrated embodiment, the meandered line 422 has a width of .065 cm and length of 1.0 cm between the input/output ports 422. Transmission line corners 423 may be mitered, 45° to minimize signal reflection and maximize signal transmission along the line 422. Spacing 424 is designed to minimize coupling between proximate line sections. In one embodiment, line spacing is .033 cm. In an alternative embodiment line spacing 424 is defined such that coupling between proximate line sections 422a, 422b is no more than -7 dB. Bio-assay 420 is formed using standard photolithographic techniques and fabricated using sputtered gold transmission lines on a .55 mm thick quartz glass substrate 425 having a dielectric constant of approx. 3. Those of skill in the art will appreciate that other signal path architectures, conductive and substrate materials, and photolithographic techniques may be alternatively employed.

Paragraph beginning at page 24, line 23:

Fig. 4C illustrates a top view of a ring resonator bio-assay 430 for use with the test fixture of Fig. 3A. The bio-assay 430 includes input/output ports 431a and 431b coupled to a ring resonator 434. Ring resonator 434 includes three concentric rings 434 a-c and a solid

circular ring 434d disposed therein. Each ring 434a-c has a width of .1 cm and is separated from proximate ring(s) by a spacing of .1 cm. The solid circular element 434d is .050 cm in radius and is disposed at the ring center. In alternative embodiments, spacing 434e and/or widths may vary from ring to ring. Bio-assay 430 is formed using standard photolithographic techniques and fabricated using sputtered gold transmission lines on a .55 mm thick quartz glass substrate 435 having a dielectric constant of approx. 3. Those of skill in the art will appreciate that other signal path architectures, conductive and substrate materials, and photolithographic techniques may be alternatively employed.

Paragraph beginning at page 26, line 20:

Fig. 4D illustrates a top view of a capacitive gap bio-assay 440 for use with the test fixture of Fig. 3A. Bio-assay 440 includes an input port 441a coupled to an input line segment 442a and an output port 441b coupled to an output line segment 442b. Disposed between the input and output line segments 442a and 442b is a gap 444 where the sample is deposited during testing. In the illustrated embodiment, input and output line segments 442a and 442b are each .495 mm long and .250 mm wide. Capacitive gap 444 measures .010 mm x .250 mm. Bio-assay 440 is formed using standard photolithographic techniques and fabricated using sputtered gold transmission lines on a .55 mm thick quartz glass substrate 445 having a dielectric constant of approx. 3. Those of skill in the art will appreciate that other signal path architectures, conductive and substrate materials, and photolithographic techniques may be alternatively employed.

Paragraph beginning at page 26, line 31:

During normal operation without an applied sample, a test signal is injected into the port 441a through, for example, an SMA connector 360 as shown in Fig. 3B. Via electromagnetic coupling, a portion of the test signal's electromagnetic field propagates across the capacitive gap 444 between the input and output line segments 442a and 442b. The capacitive gap 44 prevents the transmission of D.C. voltage and current from passing between the input and outputs. The test signal is then recovered at the output port 441b for processing. The width and separation of the gap 444, impedances of input and output line segments 442a and

442b, the dielectric constant of the substrate 445, and the frequency of operation will influence the amount of signal power transferred between the input and output ports 441a and 441b. The bio-assay capacitive gap circuit 440 will exhibit a signal response which varies over a test frequency range.

Paragraph beginning at page 28, line 9:

When a sample 456 is applied over the dielectric region 455, a longitudinal MBR 457 is formed along the surface of the insulating substrate 453. The formed MBR serves as a signal path for the test signal. As described above, the MBR 457 exhibits a dielectric property which modulates the test signal and each MBR 457 will exhibit a different dielectric property which will in turn modulate the test signal differently. The modulated signals or "signatures" are largely unique and can be associated with samples having known molecular binding events. These stored signals can later be used to identify the molecular structure in an unknown solution. Molecular structures within the same class may exhibit a similar frequency pattern over a common test frequency range. In this case, the tester is able to identify the class of the unknown molecular structure if the identity of the molecular structure is known.

Paragraph beginning at page 29, line 11:

In one embodiment, measurement system 540 may consist of the previous described measurement system 240 (S-parameter module 542 and network analyzer system 544) or any of the alternative embodiments described herein. Similarly, input and output test cables 524a and 524b, control bus 570 ~~550~~, and computer 560 may consist of those previously described and/or their alternatives.

Paragraph beginning at page 30, line 3:

As explained, the bio-assay array 700 may be fabricated in wafer form using semiconductor processing techniques. In this embodiment, the array test system 500 may consist of a wafer probe test station, such as those manufactured by Cascade Microtech, Inc. of Beaverton, Oregon (www.cascademicrotech.com) which includes or is coupled to the aforementioned input and output switches 530 and 550, and computer 560. The wafer probe

station utilizes one or more probe cards, each of which is capable of providing a large number of low loss, low VSWR signal interconnections to the bio-assay array.

Paragraph beginning at page 30, line 24:

Fig. 6A illustrates a side view of one possible embodiment of the NxM array test fixture 600 in accordance with the present invention. Similar in construction to the single path test fixture 300 shown in Fig. 3, test fixture 600 includes a top plate 602, bottom plate 604, and a sample cavity 640 (having top and bottom recesses 640a and 640b, respectively) which holds the aforementioned reaction vessel 610, bio-assay device 700 (further described in Fig. 7 below), and bottom spacer 630 elements. In the illustrated embodiment, the supplied sample is contained on the top surface of the bio-assay device in recess 618 of the reaction vessel 610. In the NxM array test fixture embodiment, the dimensions of sample cavity 640 and correspondingly reaction vessel 610 and bottom spacer 630 are designed to accommodate the bio-assay device 700 which may be larger or smaller than the bio-assay device 300 shown in Fig 3. Each array element includes a small, monolithically deposited structure to form a recessed area over the signal path in order to hold a portion of the applied sample in electromagnetic communication with the signal path of each array element. In another embodiment, MEMS (micro-electronic machining systems) technology may be used to fabricate the sample cavity at the bio-assay device level.

Paragraph beginning at page 31, line 29:

Figure 7A illustrates one embodiment of an integrated bio-assay array 700 in accordance with the present invention. The integrated array 700 is supplied with a test signal via the signal source of measurement system 540. The array 700 includes an integrated 1xN input switch 702a and Mx1 output switch 704 which are monolithically formed during the semiconductor fabrication process. The number of inputs may be the same as the number of outputs in which case M=N, the number of inputs and outputs may differ.

Paragraph beginning at page 32, line 1:

The 1xN input switch 702 routes the incoming test signal to the desired array element within array 703. The MBR in the array element 703_j modulates the test signal according to the dielectric properties of the molecular binding events which make up the MBR. An Mx1 output switch 704 ~~550~~ routes the modulated test signal to a detector of the measurement system 540. An analyzer of the measurement ~~test~~ system 540 compares the input and modulated test signals to determine the measured signal response. While each array element 703_j is illustrated as a two-port device, those of skilled in the art will appreciate that one-port or multiple port array elements may be used alternatively.

Paragraph beginning at page 32, line 9:

As explained above, the array 703 ~~700~~ and the input and output switches 702 and 704 may be fabricated either as discrete components or in wafer form and integrated in varying degrees depending upon the application. In the illustrated embodiment, the array 700 and input and output switches are monolithically formed on a semiconductor wafer. In another embodiment, the input and output switches 702 and 704 are monolithically formed separately from the array 703 ~~700~~ and connected via wire or ribbon bonds. In a further embodiment, input and output switches 702 and 704 ~~530 and 550~~ and array 703 ~~700~~ are each discrete units. Those skilled in the art will appreciate that other arrangements are also possible.

Paragraph beginning at page 32, line 24:

In the embodiment of Fig. 7B, the source and drain terminals 712 and 714 of FET 710 are employed as the input and output ports, 711 and 715 respectively and the on/off state of the FET 710 is controlled via a voltage applied to the gate terminal 714. The sample is applied over FET 710 such that the MBR 716 provides a parallel path between the source and drain terminals 712 and 714. FET 710 is designed such that when turned off, it presents a drain to source resistance (R_{ds}) which is much higher than resistance through the MBR 716. In this instance, the signal path propagates through the MBR 716 which modulates the test signal. The modulated test signal is recovered (through a DC blocking capacitor to remove the DC bias) and

compared to the input test signal to detect and/or identify the molecular binding events occurring within the MBR 716. When the FET 710 is activated, it provides a much lower R_{ds} compared to the resistance of the MBR 716. In this instance, the MBR 716 is effectively switched out of the signal path and the signal propagates largely unaffected by it. Thus by simply opening or closing a switch, an array element may be addressed.

Paragraph beginning at page 33, line 3:

Fig. 7C illustrates a further embodiment of a FET used as an array element which is optically switched. FET 720 is connected similarly to FET 710 described in Fig. 7B and may consist of a photosensitive transistor, diode or other photosensitive device. The gate junction 722 may be illuminated, for instance, with normal sunlight, a laser, a Light Emitting Diode (LED), or other source having a wavelength to which FET 720 has a high sensitivity. The incident light activates FET 720 to switch out the MBR 722. When the FET 720 is deactivated, the test signal propagates from FET 721 to FET output 723 through the MBR 722 and is modulated thereby. The modulated test signal is recovered (through a DC blocking capacitor not shown) and analyzed to determine the presence and/or identity of molecular binding events within the MBR 722.

Paragraph beginning at page 33, line 19:

As described above, addressable switches 753a and 753c operate to switch in and out the sample regions 753b and 753d between a signal source 751 and a signal detector 756 via input switch 752 and output switch 755. Thus, a particular row is made into a transmission path in which a single assay site appears as an impedance mismatch. Each assay site can be either switched into the circuit, or switched out of the circuit, as desired. The nature of the impedance mismatch is a function of binding and other changes in the MBR. Additional signal paths such as signal path 754 (having addressable switches 754a and 754c connected in parallel to sample regions 754b and 754d) may be included in the array and cross-strapped to the other paths using other low loss switches (not shown) to allow the test signal to propagate between signal paths 753 and 754. Input and output switches 752 and 755 are used to inject and recover the test signal

to/from the array 750. As those of skill in the art will appreciate, the described array may be extended to any number of NxM elements to provide a two dimensional array device.

Paragraph beginning at page 33, line 30:

Fig, 7E illustrates the circuit equivalent model of the array shown in Fig. 7D. The input source 751, input switch 752, output switch 755, and signal detector 756 are as illustrated in Fig. 7E. The switch impedance *Zs* is designed to be a close match with the reference impedance of the signal path *Zo*, and the assay impedance $Z^{I,J}$ is designed to be much different than either the switch or reference impedance. Thus, small changes in the assay impedance will dominate the electrical properties of any given row, and will therefore be easily detectable. The exact values for the impedances will depend on the design criteria for the particular array, but certain general principles of engineering apply, such as the greatest efficiency in terms of delivering power to the load (detector) is obtained with matched-impedance design, and reference impedances are frequently taken to be 50Ω.

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